be found in the specification, *inter alia*, at page 6, lines 9-11. Also, claim 78 has been amended to correct a typographical error by adding a period to the end of the claim. Finally, claims 78, 79 and 80 have been amended to change reference to "the modified nucleotides" to "the template-deficient nucleotides." This was done to make the reference to the nucleotides consistent with antecedent language in the claims. Applicants submit that this amendment does not change the scope of the claim and was not made for any reason related to patentability.

No new matter has been added by these amendments; therefore, Applicants respectfully request that examination continue on the claims as amended herewith.

A marked-up version of the amended claims is attached to this Amendment as a separate sheet as required by 37 C.F.R. § 1.121(c)(1)(ii). A copy of all of the pending claims as they are believed to have been amended is attached to this Amendment as an appendix. This copy of all of the pending claims is provided only as a convenience and is not intended to be an amendment of the claims pursuant to 37 C.F.R. § 1.121(c)(3).

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 1-19, 21-23, 27, 31-45, and 77-80 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Specifically, the Office Action alleged that claims 1, 21-23, 44, 45, 77, 79, and 80 merely recited a use without any active, positive steps delimiting how this use is actually practiced, and it was therefore unclear what methods Applicants intended to encompass. Further, the Office Action similarly rejected claims 2-19, 27, 31-45, and 78, which depend from independent claims 1, 23, 77, 79, and 80. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended. Claims 1, 23, and 77-80 have been amended herewith to recite the step of "conducting a nucleic acid amplification reaction." Accordingly, the rejection of claims 1, 23, and 77-80, and those claims dependent thereon, under 35 U.S.C. § 112, second paragraph, is believed to be obviated.

The Office Action also rejected claims 1-19, 21-23, 27, 31-45, 77-80 under 35 U.S.C. § 101 because the claims allegedly recited a use without setting forth any steps involved in the process. As noted above, claims 1, 23, and 77-80 have been amended herewith to recite the step

of "conducting a nucleic acid amplification reaction." Therefore, this rejection is believed to be obviated.

Further, the Office Action rejected claim 78 under 35 U.S.C. § 112 because the claim did not end with a period. Claim 78 has been amended herewith to correct this typographical error.

The Office Action rejected claims 77 and 80 under 35 U.S.C. § 112 because the claims allegedly did not have appropriate antecedent basis for the phrase "two or more adjacent template-deficient nucleotides." Claims 77 and 80 have both been amended herewith to correct the typographical error where the phrase "two or more" was mistakenly used instead of the phrase "one or more."

Rejection Under 35 U.S.C. § 102

Claims 1, 5, 8-10, 19, 22, and 77 were rejected under 35 U.S.C. § 102(a), (e) as being anticipated by Wallace *et al.* (US Patent 6,027,923). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The rejection asserts that Wallace *et al.* discloses the use of primers that contain a non-replicable element in a nucleic acid amplification reaction. While this statement is generally correct, the Examiner misconstrues the particular amplification processes disclosed in Wallace *et al.* and arrives at an overly broad interpretation of the composition of primers disclosed therein. In particular, the Office Action asserts that the primers disclosed in Wallace *et al.* are used in "repeated rounds of amplification," citing Wallace *et al.* at col. 2, lines 44-48. Such an assertion is inaccurate because it equates a successive round of amplification with a successive generation of a primer extension product. It is important to note that the primers of Wallace *et al.* are used to generate **only** first and second generation primer extension products. *See* Wallace *et al.* at col. 2, lines 44-48. Significantly, no third generation primer extension products are produced in Wallace *et al.*, even though there may be three or more "rounds of amplification." For example, if there were, say, five rounds of amplification according to the methods of Wallace *et al.*, no fifth generation primer extension product would be produced, just more first and second generation primer extension products. In other words, while the primers disclosed in Wallace *et al.* may repeatedly prime the replication of an original template DNA strand to produce first

generation primer extension products, and repeatedly prime the replication of a first generation primer extension product to produce second generation primer extension products, there is no production of a third (or higher) generation primer extension product because second generation primer extension products "cannot serve as templates for the synthesis of extension products." Wallace *et al.* at col. 2, lines 49-53. The fact that the primers disclosed in Wallace *et al.* do not and cannot prime the replication of second (or higher) generation primer extension products is evidence of why they do not anticipate the claimed invention; this is more fully explained below.

The present claims recite the use of a template-deficient oligonucleotide as a primer where "the number and composition of template-capable nucleotides 3' of the template-deficient nucleotide closest to the 3'end of the template-deficient oligonucleotide is sufficient to allow the template-capable nucleotides 3' of the template-deficient nucleotide closest to the 3' end **alone** to effectively prime nucleic acid synthesis in the nucleic acid amplification reaction" (emphasis added). In contrast, Wallace *et al.* discloses primers where the number and composition of nucleotides 3' of a template-deficient nucleotide is **insufficient** to effectively prime nucleic acid synthesis. That is, the primers disclosed in Wallace *et al.* can prime nucleic acid synthesis only with nucleotides that are **both 5' and 3'** of a template-deficient nucleotide. This is why, as discussed above, the second generation primer extension products of Wallace *et al.* are incapable of serving as templates for the primer extended to prepare its first generation template. *See* Wallace *et al.*, *inter alia*, at the paragraph bridging cols. 5 and 6. If the primers of Wallace *et al.* possessed nucleotides 3' of a template-deficient nucleotide that **alone** could effectively prime nucleic acid synthesis, then they would hybridize to the second generation primer extension product and prime the synthesis of a third generation primer extension product. In that case, the second generation primer extension product would serve as a template for replication, which is a result the methods of Wallace *et al.* specifically were designed to prevent.

Consider also the figures of Wallace *et al.* As can be seen from Fig. 1, the target sequence strands (solid lines) and first generation primer extension products (dotted lines) can both be primed by primers (dashed lines) that contain a template-deficient nucleotide (either an "x" or "o"). However, the second generation primer extension products (strands 10 and 20 in Fig. 2 and the third and fifth strands in Fig. 3 of Wallace *et al.*) are not primed by the Wallace *et*

al. primers. The reason these second generation primer extension products are not primed and replicated to produce third generation primer extension products is because the primers disclosed in Wallace *et al.* can only bind to and prime when nucleotides 5' of the template-deficient nucleotide ("x" or "o") are involved in hybridization. That is, the nucleotides 3' of the template-deficient nucleotide in the primers of Wallace *et al.* alone are not able to effectively prime nucleic acid synthesis **by design**. The result is that only first and second generation primer extension products are produced, no matter how many replication cycles are conducted. Accordingly, because the primers disclosed in Wallace *et al.* do not contain the number and composition of template-capable nucleotides 3' of the template-deficient nucleotide closest to the 3' end that alone are sufficient to effectively prime nucleic acid synthesis, Wallace *et al.* does not anticipate the claimed invention.

Rejection Under 35 U.S.C. § 102/103

Claims 1-19, 21-23, 27, 31-45, and 77-80 were rejected under 35 U.S.C. § 102(e) as being anticipated by or, in the alternative under 35 U.S.C. § 103(a) as being obvious over Van Ness *et al.* (US Patent 6,361,940). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Office Action asserts that Van Ness *et al.*, at columns 82-85, discloses performing amplification reactions where one or more abasic nucleotides are incorporated into a primer. However, Van Ness *et al.* does not disclose primers that contain abasic sites where the number and composition of nucleotides 3' of the abasic site closest to the 3' end is alone sufficient to effectively prime nucleic acid synthesis. This is more fully detailed below.

The Office Action emphasized that in Table 14 and column 84 of Van Ness *et al.* at least one of the primers contains modified nucleotides located at the 5' terminus and within three nucleotides of the 5' terminus. Applicants respectfully submit, however, that the Examiner has misidentified the abasic primers disclosed in Van Ness *et al.* Specifically, in the primers disclosed in column 84, "dS" represents the abasic dSPACER nucleotide and "dN" represents deoxynebularine. *See* Van Ness *et al.* at col. 85, lines 4-5. As can be seen from the sequences listed in column 84, lines 47-49, primers H17, H14, and H11 do not contain any abasic or

modified nucleotides because there are no "dS" or "dN" present in the primer sequences. Further, in Table 14, Van Ness *et al.* discloses that these particular primers only contain mismatchs and are without any substitutions. Thus, primers H17, H14, and H11 of Van Ness *et al.* do not contain any template-deficient nucleotides, as recited in the present invention.

As for the remaining primers listed in column 84 and in Table 14 of Van Ness *et al.*, none of them possess the number and composition of nucleotides 3' of the template-deficient nucleotide closest to the 3' end that is **alone** sufficient to effectively prime nucleic acid synthesis. For example, primers AB1-3, which contain the abasic nucleotide "dS," do not prime nucleic acid synthesis. *See* Van Ness *et al.* at Table 14. Primers DN1-6, on the other hand, do prime nucleic acid synthesis, but importantly these particular primers do not contain the abasic nucleotide "dS." Instead, they contain "dN," which is a nucleotide that polymerases can read through. *See* Van Ness *et al., inter alia,* at col. 58, lines 33-41. Accordingly, "dN" or deoxynebularine is not a template-deficient nucleotide as recited in the present invention. Therefore, because Van Ness *et al.* does not disclose primers as those recited in the claimed invention, the claimed invention is novel over this reference.

Moreover, there is no motivation, suggestion, or other teaching in Van Ness *et al.* to use a template-deficient oligonucleotide as a primer in a nucleic acid amplification reaction where the number and composition of template-capable nucleotides 3' of the template-deficient nucleotide closest to the 3' end can alone effectively prime nucleic acid synthesis. Rather, Van Ness *et al.* teaches only the insertion of an abasic nucleotide or deoxynebularine into an oligonucleotide to improve priming specificity since these nucleotides decrease the helical coil transition temperature (HCT) of the oligonucleotide. *See* Van Ness *et al.*, *inter alia*, at Example 6, Table 12. However, for the primers in Van Ness *et al.* where an abasic nucleotide was inserted, none of them were effective at priming nucleic acid synthesis. Thus, Van Ness *et al.* teaches that deoxynebularine, which is not a template-deficient nucleotide, should be inserted into primers. *See* Van Ness *et al.* at col. 85, lines 65-68. Therefore, since nothing in Van Ness *et al.* can be taken to motivate or suggest to one of ordinary skill in the art the use of oligonucleotides that contain nucleotides 3' of a template-deficient nucleotide closest to the 3' end that can alone effectively prime nucleic acid synthesis, the present invention is patentable over this reference.

Claim Objections

Claim 21 was objected to under 37 C.F.R. § 1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. In this Amendment, claim 21 has been amended to correct an error relating to its dependency and the claim now depends from claim 1. Therefore, this objection is believed to be obviated.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A Credit Card Payment Form PTO-2038 authorizing payment in the amount of $205.00, for the fee for a small entity under 37 C.F.R. § 1.17(a)(2) and a Request for a Two-Month Extension of Time are enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees that may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,
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CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence, including any items indicated as attached or included, is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231, on the date indicated below.

Robert A. Hodges

1/10/2003
Date